



TITLE:

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AUTHOR(S):

Inagaki, Nobuya; Sano, Hiroki; Seki, Yoshifumi; Kuroda, Shingo; Kaku, Kohei

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Efficacy and safety of once-weekly oral trelagliptin switched from once-daily dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes mellitus: An open-label, phase 3 exploratory study

Nobuya Inagaki^{1*} , Hiroki Sano², Yoshifumi Seki², Shingo Kuroda², Kohei Kaku³

¹Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, ²Takeda Development Center Japan, Takeda Pharmaceutical Company Limited, Osaka, and ³Department of Internal Medicine, Kawasaki Medical School, Okayama, Japan

Keywords

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*Correspondence

Nobuya Inagaki
Tel.: +81-75-751-3562
Fax: +81-75-771-6601
E-mail address:
inagaki@kuhp.kyoto-u.ac.jp

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ABSTRACT

Introduction: Trelagliptin, a novel once-weekly oral dipeptidyl peptidase-4 (DPP-4) inhibitor, has shown favorable efficacy and safety in type 2 diabetes mellitus patients. Trelagliptin was launched in Japan, and is expected to be initially used for switchover from a daily DPP-4 inhibitor in the clinical setting. Thus, the present study was carried out to explore the efficacy and safety of trelagliptin after a daily DPP-4 inhibitor was switched to it.

Materials and Methods: This was an open-label, phase 3 exploratory study to evaluate the efficacy and safety of trelagliptin in Japanese type 2 diabetes mellitus patients who had stable glycemic control on once-daily sitagliptin therapy. Eligible patients received trelagliptin 100 mg orally before breakfast once a week for 12 weeks. The primary end-point was blood glucose by the meal tolerance test, and additional end-points were glycemic control (efficacy) and safety.

Results: Altogether, 14 patients received the study drug. The blood glucose did not markedly change from baseline at major assessment points in the meal tolerance test, and a decrease in blood glucose was observed at several other assessment points. Adverse events were reported in 42.9% (6/14) of patients, but all adverse events were mild or moderate in severity, and most were not related to the study drug. No cases of death, serious adverse events or hypoglycemia were reported.

Discussion: It is considered possible to switch a once-daily DPP-4 inhibitor to trelagliptin in type 2 diabetes mellitus patients with stable glycemic control in combination with diet and exercise therapy without any major influences on glycemic control or safety.

INTRODUCTION

Poor medication adherence is a common issue in clinical practice, particularly with chronic asymptomatic diseases, such as type 2 diabetes mellitus, dyslipidemia and hypertension^{1–4}. In patients with type 2 diabetes mellitus, it is important to improve medication adherence to maintain favorable glycemic control during long-term treatment^{3–6}. Reducing the frequency

of dosing with newer drugs could provide patients with better control by improving their adherence to medications, especially when the medical condition tends to be chronic, as with type 2 diabetes mellitus. More than two-thirds of patients with type 2 diabetes mellitus comply poorly with prescribed oral antidiabetic medications, and adherence is improved by decreasing the frequency of administration^{7–11}. One of the major causes of low medication adherence is inconvenience associated with frequent dosing. In fact, a questionnaire survey carried out in

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Japan on expectations for new antidiabetic drugs in patients with type 2 diabetes mellitus receiving an oral hypoglycemic agent(s) showed that approximately 70% of the patients wished for less frequent dosing¹².

Trelagliptin succinate (trelagliptin) is a novel, long-acting, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor that is suitable take once a week^{13–15}. A phase 2 study using once-weekly trelagliptin at doses ranging from 12.5 to 200 mg in patients with inadequately controlled type 2 diabetes mellitus showed significantly greater reductions in glycosylated hemoglobin A1c (HbA1c) in the trelagliptin group compared with the placebo group, and dose-dependency in HbA1c in the trelagliptin group with favorable safety and tolerability profiles¹³. A phase 3, randomized, double-blind, active-controlled study of 24-week treatment with oral administration of trelagliptin 100 mg once a week showed non-inferiority of trelagliptin to the once-daily DPP-4 inhibitor, alogliptin, with favorable safety and tolerability profiles comparable with those of alogliptin¹⁴. A phase 3, open-label, long-term study of 52-week treatment with trelagliptin 100 mg once a week as monotherapy or in combination with an existing oral antidiabetic drug showed well-tolerated long-term safety and efficacy both with monotherapy and combination therapies¹⁵.

In the clinical setting, it is expected that this newly developed once-weekly DPP-4 inhibitor, trelagliptin, will initially be used as a switchover from a daily DPP-4 inhibitor. Therefore, the present study was carried out to explore the efficacy and safety of trelagliptin after a daily DPP-4 inhibitor was switched to it.

MATERIALS AND METHODS

Study design and patients

This was a single-center, open-label, phase 3 exploratory study to evaluate the effect on blood glucose when the once-daily DPP-4 inhibitor, sitagliptin 50 mg, was switched to the once-weekly oral trelagliptin 100 mg in Japanese type 2 diabetes mellitus patients with stable glycemic control on sitagliptin therapy along with diet and exercise therapy. The study comprised a 2-week screening period, a 12-week treatment period and a 1-week follow-up period (15 weeks in total).

Patients visited the study site at week –2 (start of the screening period), and were hospitalized from day –2 to day 4. After they were discharged from the study site, patients visited the study site on day 7, and at weeks 2, 4, 8 and 12 during the treatment period, and week 13 (end of the follow-up period). During the 12-week treatment period, all patients received oral administration of trelagliptin 100 mg once a week. Patients were required to adhere to a certain diet and exercise therapy (if any) for the entire study period, and the investigators instructed the patients on the prescribed calorie intake and exercise program throughout the study period. The sample size was a total of 14 patients who received the study drug.

Eligible patients were adults aged ≥ 20 years who had been given a diagnosis of type 2 diabetes mellitus, were adhering to a certain diet and exercise therapy, and had received sitagliptin

50 mg/day for at least 10 weeks before the start of the screening period, whose HbA1c values were stable between 6.2 and 8.4% at the start of the screening period, and fluctuated within a level of $\leq 5.0\%$ from the level at the visit before the start of the screening period and the start of the screening period. Patients were excluded if they received any antidiabetic drugs other than sitagliptin (50 mg/day) within 10 weeks before the start of the screening period or during the screening period. Patients were also excluded if they had a fasting plasma glucose (FPG) of <70 mg/dL or ≥ 250 mg/dL at the start of the screening period, if they had signs of hepatic impairment (e.g. alanine aminotransferase or aspartate aminotransferase ≥ 2.5 -fold the upper limit of normal, or total bilirubin of ≥ 34.2 mmol/L), or if they had electrocardiogram abnormalities (e.g., QT interval corrected for heart rate [QTcF interval] >450 ms).

The present study, including the protocol, was reviewed and approved by the institutional review board at the clinical site, and was carried out in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation E6 (R1) Guidelines for Good Clinical Practice, and all applicable local laws and regulations. All patients provided written informed consent.

Assessment

The primary end-point was blood glucose measured during the meal tolerance test, which was carried out before each meal, 2 h after starting each meal, and 4.5 h after starting dinner on day –1, day 1, day 2 and day 3, and before breakfast and 2 h after starting breakfast on day 7. The nutritional composition of the test meals was approximately 25% protein, 60% carbohydrate and 15% fat. The composition was the same for all test meals and for all patients. The calorie of each test meal was determined for each patient, and kept within a range of 10% variation from the baseline calorie intake of each patient. During the hospitalization period for the tests, patients were not allowed to consume anything other than the designated meals, except for some beverages that do not affect the evaluation of blood glucose, and had to follow the instructions on exercise therapy (if any).

Additional end-points were efficacy variables, such as HbA1c, FPG, glycoalbumin, DPP-4 activity, bodyweight, and insulin, glucagon and active glucagon-like peptide-1 (GLP-1) concentrations measured during the meal tolerance test. Safety end-points included adverse events (AEs), vital signs, 12-lead electrocardiogram and clinical laboratory test results. Clinical laboratory tests were carried out at an independent central laboratory (LSI Medience Corporation, Tokyo, Japan). HbA1c was converted from the Japan Diabetes Society values (%) to the National Glycohemoglobin Standardization Program values (%) using the following formula to calculate: National Glycohemoglobin Standardization Program HbA1c (%) = $1.02 \times$ Japan Diabetes Society HbA1c (%) + 0.25%. DPP-4 activity was measured by the enzyme activity measurement method, and active GLP-1 was measured with Glucagon-Like Peptide-1 (Active) ELISA kit

96-well plate (Merck Millipore, Darmstadt, Germany; recovery: >60%; intra-assay variation: <15%).

Statistical analysis

Efficacy evaluation was carried out on the full analysis set, comprising all patients who received at least one dose of the study medication. All variables were summarized using descriptive statistics (number of individuals; mean; standard deviation; maximum, minimum and quartile values) and two-sided 95% confidence intervals for the mean values.

Safety evaluation was carried out on the safety analysis set, including all patients who received at least one dose of the study medication, and no statistical inference was made for safety analyses. A treatment-emergent AE (TEAE) was defined as an AE of which the date of onset was on or after the start of study medication. TEAEs were summarized and displayed using the *Medical Dictionary for Regulatory Activities*-preferred terms. Other safety data were summarized using descriptive statistics and a shift table.

The planned number of participants was set as 14 who received the study drug, considering the feasibility of this study. This planned sample size was not based on statistical consideration.

All statistical analyses were carried out with SAS, version 9.2 (SAS Institute, Cary, NC, USA).

The study was registered with ClinicalTrials.gov, number NCT01751360.

RESULTS

The present study was carried out from 5 January 2013 to 8 August 2013. A total of 18 patients signed informed consent, and of these, 14 patients received the study drug, and all of them completed the study. The rate of compliance with trelagliptin was 99.45% up to week 12.

The demographic and baseline characteristics of patients in full analysis set are shown in Table 1.

For blood glucose measured during the meal tolerance test, the mean changes from baseline and the two-sided 95% confidence intervals at each assessment point on days 1, 2, 3 and 7 are shown in Table 2. The mean change in the pre-breakfast and 2-h post-breakfast blood glucose from baseline was -6.2 to -0.4 mg/dL and -8.7 to 7.0 mg/dL, respectively, on days 1, 2, 3 and 7. The mean change in pre-lunch and 2-h post-lunch blood glucose from baseline was -4.1 to 0.4 mg/dL and -36.4 to -10.6 mg/dL, respectively, on days 1, 2 and 3. The mean change in pre-dinner, 2-h post-dinner, and 4.5-h post-dinner blood glucose from baseline was -10.4 to 3.4 mg/dL, -16.4 to 12.1 mg/dL and -14.6 to 4.5 mg/dL, respectively, on days 1, 2 and 3.

The mean changes in HbA1c, FPG, glycoalbumin and body-weight from baseline, and the two-sided 95% confidence intervals at the end of the treatment period are shown in Table 3.

The mean change in HbA1c, FPG, and glycoalbumin from baseline at the end of the treatment period was 0.04%, -1.6

Table 1 | Demographic and baseline characteristics

Characteristic/category	Overall <i>n</i> = 14
Age (years)	64.9 (4.92)
Age categories (years)	
<65	5 (35.7)
≥65	9 (64.3)
Sex	
Male	12 (85.7)
Female	2 (14.3)
Height (cm)	166.5 (8.83)
Bodyweight, day 1 (kg)	64.14 (8.11)
BMI, day 1 (kg/m ²)	23.08 (1.75)
Duration of T2DM (months)	108.4 (57.44)
Creatinine clearance, day 1 (mL/min)	85.3 (15.37)
HbA1c, day 1 (%)	7.06 (0.49)
FPG, day 1 (mg/dL)	140.5 (23.25)
2-h post-breakfast blood glucose, day -1 (mg/dL)	202.1 (38.30)

Values represent the mean (standard deviation), except for age categories and sex, for which the number of patients (%) is presented. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; T2DM, type 2 diabetes mellitus.

mg/dL and 1.01%, respectively. The mean change in body-weight from baseline at the end of the treatment period was 0.39 kg.

The mean change in insulin, glucagon and active GLP-1 concentration from baseline at each assessment point (before each meal, 2 h after starting each meal and 4.5 h after starting dinner) of the meal tolerance test showed that insulin, glucagon, and active GLP-1 concentration did not markedly change at most assessment points during the treatment period (data not shown).

During the treatment period, 42.9% (6/14) of patients experienced at least one TEAE (Table 4). All of the TEAEs were mild (35.7% [5/14 patients]) or moderate (7.1% [1/14 patients]) in severity. No cases of death, serious TEAEs or TEAEs leading to discontinuation of the study drug were reported. No cases of hypoglycemia were reported. The only acute pancreatitis-related TEAE reported was increased lipase, which occurred in only one out of 14 patients (7.1%) and was mild in severity. It was considered to be related to the study drug.

DISCUSSION

Trelagliptin was approved in March 2015 and has been launched in Japan. The evidence available to date for trelagliptin suggests that it is effective with dosing once a week. In the phase 1 study, a single dose of trelagliptin (3.125–800 mg) had an area under the plasma concentration–time curve from time zero to infinite time and maximum concentration that were generally dose-proportional, the median time to reach peak concentration was 1.0–1.5 h, and the elimination half-life in the elimination phase was 38.44–54.26 h. Findings from the

Table 2 | Changes in blood glucose measured during the meal tolerance test

Assessment point	Day -1 (observed value) n = 14	Day 1 (change) n = 14	Day 2 (change) n = 14	Day 3 (change) n = 14	Day 7 (change) n = 14
Before breakfast					
Mean (SD)	140.9 (23.70)	-0.4 (6.71)	-6.2 (5.42)	-3.0 (7.98)	-1.7 (13.21)
Two-sided 95% CI	[127.18, 154.54]	[-4.23, 3.52]	[-9.35, -3.08]	[-7.61, 1.61]	[-9.34, 5.91]
2 h after starting breakfast					
Mean (SD)	202.1 (38.30)	-4.4 (17.88)	-1.6 (30.78)	7.0 (31.93)	-8.7 (25.38)
Two-sided 95% CI	[179.96, 224.18]	[-14.75, 5.89]	[-19.41, 16.13]	[-11.43, 25.43]	[-23.37, 5.94]
Before lunch					
Mean (SD)	139.9 (39.19)	-3.7 (22.33)	0.4 (17.98)	-4.1 (12.99)	NA
Two-sided 95% CI	[117.23, 162.49]	[-16.61, 9.18]	[-9.95, 10.81]	[-11.57, 3.43]	
2 h after starting lunch					
Mean (SD)	217.4 (49.07)	-10.6 (18.13)	-36.4 (24.81)	-28.1 (27.58)	NA
Two-sided 95% CI	[189.03, 245.69]	[-21.11, -0.17]	[-50.68, -22.03]	[-44.07, -12.22]	
Before dinner					
Mean (SD)	141.2 (40.82)	-4.6 (19.76)	-10.4 (25.41)	3.4 (23.71)	NA
Two-sided 95% CI	[117.65, 164.78]	[-15.98, 6.84]	[-25.10, 4.24]	[-10.33, 17.04]	
2 h after starting dinner					
Mean (SD)	229.1 (55.70)	12.1 (17.67)	-16.4 (26.89)	-13.2 (35.11)	NA
Two-sided 95% CI	[196.98, 261.30]	[1.87, 22.27]	[-31.95, -0.90]	[-33.49, 7.06]	
4.5 h after starting dinner					
Mean (SD)	179.0 (49.48)	4.5 (28.27)	-14.0 (28.12)	-14.6 (29.64)	NA
Two-sided 95% CI	[150.43, 207.57]	[-11.82, 20.82]	[-30.23, 2.23]	[-31.76, 2.47]	

Units are in mg/dL. CI, confidence interval; NA, not applicable; SD, standard deviation.

Table 3 | Changes from baseline at the end of the treatment period in efficacy measures

Variable	Summary Statistics		95% CI	
	Mean	SD	Lower	Upper
HbA1c (%)	0.04	0.36	-0.16	0.25
FPG (mg/dL)	-1.6	13.93	-9.61	6.47
Glycoalbumin (%)	1.01	1.78	-0.02	2.03
Weight (kg)	0.39	1.14	-0.27	1.05

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c.

same study showed that inhibition of DPP-4 activity was maintained for 7 days. In a phase 2 study, trelagliptin showed a dose-dependent decrease in HbA1c at doses of 12.5–200 mg trelagliptin, which were significant vs the placebo. At 100 mg dosing, the mean rate of DPP-4 inhibition remained approximately 75–80% at 7 days after dosing¹³. In a phase 3 confirmatory study, trelagliptin showed similar efficacy and safety to alogliptin 25 mg, and the inhibition of DPP-4 in the trelagliptin 100 mg group at 7 days after dosing showed no notable differences from that in the alogliptin group at 1 day after dosing. In that confirmatory study, the mean rate of DPP-4 inhibition in each treatment group was maintained at 70% from week 2 to the end of the treatment period, and the incidence of TEAEs was similar between the trelagliptin and alogliptin groups¹⁴.

Table 4 | Incidence of all treatment-emergent adverse events

	No. patients (%) Overall n = 14
Patients with any TEAEs	6 (42.9)
Dry eye	1 (7.1)
Periodontitis	1 (7.1)
Pharyngitis	1 (7.1)
Sinusitis	1 (7.1)
Blood creatine phosphokinase increased	1 (7.1)
Blood urine present	1 (7.1)
Lipase increased	1 (7.1)
Protein urine present	1 (7.1)
Spinal osteoarthritis	1 (7.1)
Diabetic nephropathy	1 (7.1)

Data are expressed in number of patients (%). TEAEs, treatment-emergent adverse events.

Furthermore, in a phase 3 long-term study, trelagliptin showed well-tolerated long-term safety and efficacy¹⁵. These results support the potential of trelagliptin, which is suitable to be taken once a week.

More than two-thirds of patients with diabetes have inadequate adherence to oral antidiabetic therapy. Several barriers have been suggested to interfere with the treatment regimen for type 2 diabetes mellitus, such as regimen complexity as a result of multiple drugs or multiple daily doses, depression, and

remembering to take the doses and refill them^{16–19}. More than half of patients taking antidiabetic drugs daily expect that the type and number of drugs they take will be decreased. The availability of a once-weekly oral drug will provide an additional treatment option for patients with type 2 diabetes mellitus and their physicians. This was the first report of exploratory evaluation of the efficacy and safety of once-weekly trelagliptin 100 mg after the once-daily DPP-4 inhibitor, sitagliptin 50 mg, was switched to it in Japanese type 2 diabetes mellitus patients with stable glycemic control with sitagliptin in combination with diet and exercise therapy.

In the present study, the mean change from baseline in blood glucose concentrations was measured during the meal tolerance test. Blood glucose did not change markedly at major assessment points in the meal tolerance test, and a decrease in blood glucose was observed at several other assessment points (e.g., 2 h after starting lunch on days 1, 2 and 3). There were no cases of hypoglycemia. There were also no major changes in the other efficacy parameters, such as HbA1c and FPG. Regarding safety, we previously demonstrated that trelagliptin shows a similar safety profile as a once-daily DPP-4 inhibitor, alogliptin¹⁴. The present study also showed favorable safety and tolerability profiles of once-weekly oral trelagliptin after the once-daily DPP-4 inhibitor sitagliptin was switched to it, and did not show any new safety signals. These results show that trelagliptin can be initiated as a switchover from a once-daily DPP-4 inhibitor without a major influence on glycemic control and safety.

There were some limitations on generalizing the results of the present study. First, this study was carried out exploratively and involved just 14 patients, a number that was not based on statistical consideration. Second, this study was carried out as an open-label study and a control group was not set, and natural variations in patients or influence due to participation in this clinical trial with the hospitalization period from day –2 to day 4 were not taken into consideration. Finally, only Japanese patients were enrolled in this study. Therefore, a further study will be warranted to investigate the efficacy, as well as safety, in greater numbers of patients including a control group and/or a non-Japanese patient population.

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DISCLOSURE

The study was sponsored by Takeda Pharmaceutical Company Limited. NI and KK were medical advisors for the study. NI has received research funding and KK has received consultancy

fees from Takeda Pharmaceutical Company Limited. HS, YS and SK are employees of Takeda Pharmaceutical Company Limited. The sponsor was involved in the study design, protocol development, data collection, review and analysis of the data.

REFERENCES

1. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. *J Clin Epidemiol* 2001; 54: S57–S60.
2. Haynes RB, Ackloo E, Sahota N, *et al.* Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; CD000011.
3. Pladevall M, Williams LK, Potts LA, *et al.* Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care* 2004; 27: 2800–2805.
4. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004; 27: 1218–1224.
5. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; 42: 200–209.
6. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011; 33: 74–109.
7. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med* 2002; 19: 279–284.
8. Coleman CI, Limone B, Sobieraj DM, *et al.* Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012; 18: 527–539.
9. Hauber AB, Tunceli K, Yang JC, *et al.* A survey of patient preferences for oral antihyperglycemic therapy in patients with type 2 diabetes mellitus. *Diabetes Ther* 2015; 6: 75–84.
10. Kruk ME, Schwalbe N. The relation between intermittent dosing and adherence: preliminary insights. *Clin Ther* 2006; 28: 1989–1995.
11. Polonsky WH, Fisher L, Hessler D, *et al.* Patient perspectives on once-weekly medications for diabetes. *Diabetes Obes Metab* 2011; 13: 144–149.
12. Ishii H. Survey on the unmet needs of patients with type 2 diabetes. *Prog Med* 2010; 30: 2675–2679 (Japanese).
13. Inagaki N, Onouchi H, Sano H, *et al.* SYR-472, a novel once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor, in type 2 diabetes mellitus: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2014; 2: 125–132.
14. Inagaki N, Onouchi H, Maezawa H, *et al.* Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-

- inferiority study. *Lancet Diabetes Endocrinol* 2015; 3: 191–197.
15. Inagaki N, Sano H, Seki Y, *et al.* Long-term safety and efficacy of a novel once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in patients with type 2 diabetes mellitus: a 52-week open-label, phase 3 study. *J Diabetes Investig* 2016; 7: 718–726.
 16. Odegard PS, Capoccia K. Medication taking and diabetes: a systematic review of the literature. *Diabetes Educ* 2007; 33: 1014–1029.
 17. Bartels D. Adherence to oral therapy for type 2 diabetes: opportunities for enhancing glycemic control. *J Am Acad Nurse Pract* 2004; 16: 8–16.
 18. Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. *Postgrad Med* 2011; 123: 15–23.
 19. Wang L, Sun X, Du L, *et al.* Effects and patient compliance of sustained-release versus immediate-release glipizides in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *J Evid Based Med* 2011; 4: 232–241.